## REMARKS

I. Amendment to the Claims

Claims 1, 3-15, 17-36, 38-49 are currently pending, with claims 1, 20, 27, 29, 34, 35, 41, and 47 being independent. Claims 20-28 and 41-49 have been withdrawn from consideration as being directed to nonelected subject matter. Claims 1, 3-15, 17-19, 29-36, and 38-40 stand rejected.

Claims 1, 3-6, 17, and 29-35 have been amended. Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed. Specifically, support for the amendments to claims 1, 17, 29, 34, and 35 can be found, *inter alia*, in the specification at page 3, paragraph [0007]. Support for further amendments to claims 1, 3-5, 29, 34, and 35 can be found, *inter alia*, in the specification at pages 13-14, paragraph [0048]; page 14, paragraph [0050]; and page 27, paragraph [0094]. Support for the amendment to claim 6 can be found, *inter alia*, in the specification at page 30, paragraph [0104], to page 31, paragraph [0106]. Claims 30-33 have been amended for proper antecedent basis. Applicants respectfully submit that no new matter has been added by the way of these amendments. Applicants further submit that the amendments are being presented concurrently with a Request for Continued Examination. Therefore, Applicants respectfully request that entry of the above amendments and consideration of the remarks below.

Applicants make the present amendments without prejudice and solely in order to expedite allowance of this application and reserve the right to file applications directed to subject matter removed by way of the present amendments, as well as other matter disclosed in the specification.

II. Enablement Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner maintains the rejection of claims 1, 3-15, 17-19, 29-36, and 38-40 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable the method of treating, preventing, or ameliorating multiple sclerosis associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18, or other disorders associated with an IL-10 deficiency by administering to a subject an agonist of IL-21/IL-21R. Office Action, pp. 3-5. Specifically, the Examiner alleges that the specification does not enable (1) an IL-21 polypeptide, (2) an agonistic anti-IL-21R antibody, or (3) a method of "treating" a disease using an agonist of IL-21/IL-21R. *Id.* Applicants respectfully traverse this rejection.

A. IL-21 Polypeptide

The Examiner asserts that the specification does not provide sufficient guidance as to how to make the claimed genus of IL-21 polypeptides. *Id.* at p. 4. Applicants respectfully disagree.

Applicants respectfully submit that the specification provides a detailed explanation as to the meaning of "IL-21 polypeptide," specifically an "agonistic IL-21 polypeptide," and methods for making the same. *See* specification, pp. 13-14, ¶ [0048]; p. 15, ¶ [0053]; and pp. 18-23, ¶¶ [0067]-[0083]. Although the Examiner seems to indicate that the claims should be limited to a single sequence (*see* Office Action, p. 4), Applicants respectfully submit that specification adequately enables mammalian IL-21 polypeptides, such as human and murine IL-21 polypeptides. *See* specification, pp. 13-14, ¶ [0048], and pp. 18-19, ¶ [0067]. Moreover, the specification not only teaches that the agonistic IL-21 polypeptide may be a

mammalian IL-21 polypeptide, but the specification also teaches that any variant comprising a fragment of IL-21 that includes the mature IL-21, such as SEQ ID NO:2 for human IL-21, may be used. *Id.* Furthermore, the specification teaches that up to the final eight amino acids of the mature human IL-21 may be omitted, and thus, a human IL-21 polypeptide may comprise amino acids 1-122 of SEQ ID NO:2. *Id.* at p. 15, ¶ [0053]. Therefore, in the instance of human IL-21, the specification clearly teaches one of ordinary skill in the art how to make and use, for example, an IL-21 polypeptide comprising amino acids 1-122 of SEQ ID NO:2 (*Id.*), a fusion protein comprising amino acids 1-122 of SEQ ID NO:2 (*Id.* at pp. 20-22, ¶¶ [0073]-[0082]), an amino acid sequence encoded by a region of SEQ ID NO:1 that encodes a mature human IL-21 polypeptide (*Id.* at pp. 18-19, ¶ [0067]), and an amino acid sequence encoded by nucleic acids that hybridize to SEQ ID NO:1 under highly stringent conditions (*Id.* at p. 20, ¶ [0072]).

Applicants respectfully submit that one of ordinary skill in the art would be able to extrapolate the description in the specification regarding human and mouse IL-21 to other mammalian IL-21. However, solely to expedite prosecution, claims 1, 29, 34, and 35 have been amended to recite a human IL-21 polypeptide and a murine IL-21 polypeptide.

For at least these reasons, Applicants respectfully submit that the specification sufficiently enables the claimed methods and request reconsideration and withdrawal of this enablement-based rejection.

B. Agonistic Anti-IL-21R Antibody

The Examiner asserts that, although screening for an agonistic anti-IL-21R antibody that is generated from a defined sequence is routine in the art, the claims are not limited to an antibody against a specific, defined sequence of IL-21R because IL-21R allegedly encompasses structurally undefined variants. Office Action, p. 4. The Examiner also asserts that

the specification fails to teach what specific structures and sequences are required for generating agonistic anti-IL-21R antibodies since the IL-21R polypeptide is not limited to a single amino acid sequence. *Id.* The Examiner concludes that the claims encompass variants and a genus of polypeptides that allegedly are not structurally and functionally defined by the specification. *Id.* Applicants respectfully disagree.

Applicants respectfully submit that the specification provides a detailed explanation as to the meaning of an "agonistic anti-IL-21R antibody," an "antigen-binding fragment of an agonistic anti-IL-21R antibody," and methods for making the same. *See* specification, pp. 27-32, ¶¶ [0094]-[0111]. Although the Examiner seems to indicate that the claims should be limited to a single sequence (*see* Office Action, p. 4), Applicants respectfully submit that specification adequately enables mammalian agonistic anti-IL-21R antibodies, such as agonistic anti-human IL-21R antibodies and agonistic anti-murine IL-21R antibodies. *See* specification, p. 14, ¶ [0050], and p. 27, ¶ [0094]. The specification teaches that agonistic anti-IL-21R antibodies, or antigen-binding fragments thereof, bind to IL-21R. *Id.* at p. 27, ¶ [0094]. The specification further teaches that mammalian IL-21R may be any variant comprising a fragment of IL-21R that includes the mature region of IL-21R, such as amino acids 20-538 of SEQ ID NO:6 for human IL-21R. *Id.* at p. 14, ¶ [0050]. Therefore, in the instance of agonistic anti-human IL-21R antibodies, the specification clearly teaches one of ordinary skill in the art how to make and use, for example, antibodies that bind to the following: amino acids 20-538 of SEQ ID NO:6, an amino acid sequence at least 85% homologous to amino acids 20-538 of SEQ ID NO:6, an amino acid sequence encoded by a region of SEQ ID NO:5 that encodes a mature human IL-21R, an amino acid sequence at least 85% homologous to an amino acid sequence

encoded by a region of SEQ ID NO:5 that encodes a mature IL-21R, and an amino acid sequence encoded by nucleic acids that hybridize to SEQ ID NOs:5 under highly stringent conditions. *Id.*

Applicants respectfully submit that one of ordinary skill in the art would be able to extrapolate the description in the specification regarding agonistic anti-human and anti-mouse IL-21R to other mammalian agonistic anti-IL-21R. However, solely to expedite prosecution, claims 1, 29, 34, and 35 have been amended to recite an agonistic anti-human IL-21R antibody, an agonistic anti-murine IL-21R, an antigen-binding fragment of an agonistic anti-human IL-21R antibody, and an antigen-binding fragment of an agonistic anti-murine IL-21R antibody.

For at least these reasons, Applicants respectfully submit that the specification sufficiently enables the claimed methods and request reconsideration and withdrawal of this enablement-based rejection.

C. Method of "Treating" a Disease Using an Agonist of IL-21/IL-21R

The Examiner asserts that the specification is not enabling for method of "treating," which encompasses curing MS or its related symptoms. *Office Action*, p. 5.

Applicants respectfully disagree with the Examiner's assertions. However, solely to expedite prosecution of the application, Applicants presently amend claims 1, 29, 34, and 35 without prejudice. Thus, Applicants respectfully submit that the Examiner's rejection has been overcome and request reconsideration and withdrawal of this enablement-based rejection.

III. Written Description Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner maintains the rejection of claims 1, 29, 30, 32-36, and 38-40 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. *Office Action*, at pp. 6-7. The Examiner asserts that Applicants did not adequately describe a genus of IL-21 polypeptides, a genus of anti-IL-21R antibodies, and a genus of

antigen-binding fragments of the anti-IL-21R antibodies. *Id.* at p. 7. Applicants respectfully disagree.

Applicants respectfully submit that the specification adequately describes mammalian IL-21 polypeptides, agonistic anti-mammalian Il-21R antibodies, and antigen-binding fragments of anti-mammalian IL-21R antibodies for the same reasons discussed in Sections II(A) and (B) above. However, solely to expedite prosecution, claims 1, 29, 34, and 35 have been amended to recite a human IL-21 polypeptide, a murine IL-21 polypeptide, an agonistic anti-human IL-21R antibody, an agonistic anti-murine IL-21R, an antigen-binding fragment of an agonistic anti-human IL-21R antibody, and an antigen-binding fragment of an agonistic anti-murine IL-21R antibody. Therefore, Applicants respectfully submit that the Examiner's rejection has been overcome and request reconsideration and withdrawal of this written description-based rejection.

IV. Indefiniteness Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner maintains the rejection of claims 17-19 and 34-40 as allegedly being indefinite because the disclosure allegedly fails to set forth what is encompassed within the definition of "an IL-10 parameter." Office Action, pp. 7-8. Applicants respectfully traverse this rejection.

The Examiner asserts that the specification only describes examples to assay or evaluate IL-10 activity but fails to limit the specific parameters and activities of IL-10. *Id.* at p. 7. Applicants respectfully disagree.

One of ordinary skill in the art would understand the meaning of "IL-10 parameter" as set forth in the specification, and thus, would know the metes and bounds of the claims. The specification states that "IL-10 parameter" is qualitative of quantitative information

about IL-10 levels (e.g., IL-10 protein or IL-10 mRNA) or IL-10 activity. Specification, p. 5, ¶ [0014], and pp. 8-9, ¶ [0028]. In addition, one of ordinary skill in the art knew, at the time the application was filed, the various activities of IL-10 protein. *See* Smith et al., "IL-10 as a mediator in the HPA axis and brain," Journal of Neuroimmunology 100:140-148, Abstract (1999) (submitted herewith in an Information Disclosure Statement). Therefore, there is no ambiguity as to the phrase "IL-10 parameter" as defined in the specification.

For at least these reasons, Applicants respectfully submit that one of ordinary skill in the art would understand the metes and bounds of the claimed invention and respectfully request reconsideration and withdrawal of the indefiniteness-based rejection.

V. Rejection Under 35 U.S.C. § 102

The Examiner maintains the rejection of claims 1, 3, 4, 9-12, 14, and 29-34 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,605,272, issued to Novak et al. ("the '272 patent"). Office Action, pp. 8-11. Applicants respectfully traverse this rejection.

The Examiner asserts that the '272 patent is enabling for the instant claims because the '272 patent discloses the claimed method, and the issued patent prior art contains an enabling disclosure that was in the public's possession before the date of the present invention. *Id.* at p. 9. The Examiner also asserts that the '272 patent teaches the claimed method because the '272 allegedly teaches the same active step (i.e., administration of IL-21) and the same material (i.e., IL-21 polypeptide), and the same patient population (i.e., immunological disorders, including MS). *Id.* The Examiner further asserts that the '272 patent teaches that IL-21 enhances proliferation of $CD4^+$ T cells, $CD8^+$ T cells, and NK cells and regulates production of cytokines, such as increasing IL-10 and decreasing IFN-γ. *Id.* Finally, the Examiner asserts that

the limitation of ameliorating a symptom of MS, or MS associated with an IL-10 deficiency or increased IFN-γ, would be an inherent result of administering IL-21 because IL-21 enhances secretion of IL-10 and decreases IFN-γ, thereby reversing the condition of IL-10 deficiency and increased IFN-γ in MS. *Id.* at pp. 9-10. Applicants respectfully disagree.

First, Applicants respectfully submit that the '272 patent is not enabling for the presently claimed invention. In order for a prior art disclosure to be sufficient to "anticipate" an applicant's invention, the reference must contain an enabling disclosure of the applicant's desired subject matter; mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. M.P.E.P. § 2121.01 at 2100-55 (citations omitted). While the '272 patent may provide an enabling disclosure for the subject matter claimed therein, the '272 merely hypothesizes as to the therapeutic use of IL-21 in "a wide range of diseases arising form defects in the immune system." The '272 patent, col. 42, ll. 17-22. In fact, the '272 patent cannot even specify as to whether an IL-21 agonist, an IL-21 antagonist, or both, may be used. *See id.* at col. 42, ll. 27-31. The '272 patent also emphasizes, "It is important to note that these diseases are the result of a complex network of immune dysfunction." *Id.* at col. 42, ll. 22-24. Furthermore, the '272 patent never indicates how IL-21 is related to IL-10 and/or IFN-γ in this complex network of immune dysfunction. Therefore, one of ordinary skill in the art clearly would have had to undertake undue experimentation in order to achieve the claimed method of suppressing, reducing, delaying, or ameliorating a symptom of multiple sclerosis associated with an IL-10 deficiency or increased IFN-γ or an immunological disorder associated with an IL-10 deficiency.

Second, a single prior art reference must teach each and every element of a claim in order to anticipate that claim. *See* MPEP §2131 at 2100-67 (8th ed., Rev. 7)(citing *Verdegaal*

*Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Applicants respectfully submit that the '272 patent does not teach each and every element of the claimed method. The '272 may teach the administration of IL-21; however, the '272 patent does not teach the step of administering an agonistic IL-21/IL-21R. Indeed, the '272 patent does not know whether an agonist or an antagonist of IL-21 would be useful in a method of suppressing, reducing, delaying, or ameliorating MS or other IL-10-associated disorder. *See id.* at col. 42, ll. 27-31 (suggesting the use of zalpha11 or an antagonist of the Ligand to manipulate immune cells). In addition, the '272 patent does not teach the limitation of 1) an amount sufficient to suppress, reduce, delay, or ameliorate the symptom of multiple sclerosis associated with an IL-10 deficiency or increased IFN-γ (claims 1 and 29), 2) an amount sufficient to suppress, reduce, delay, or ameliorate multiple sclerosis associated with an IL-10 deficiency or increased IFN-γ (claim 29), or 3) an amount sufficient to increase IL-10 expression (claim 34). Because the '272 patent does not teach the relationship among IL-21, IL-10, and IFN-γ (see below), the '272 patent cannot possibly teach the limitation as to the amount of IL-21 needed, for instance, to increase IL-10 expression. Therefore, the '272 fails to teach each and every limitation of the claimed methods.

Third, Applicants respectfully submit that the '272 patent does not teach the regulatory relationship among IL-21, IL-10, and IFN-γ, contrary to the Examiner's assertion. Examples 41 and 42 of the '272 patent (cited by the Examiner) do not teach the use of IL-21 in treating or ameliorating MS or immunological disorder associated with an IL-10 deficiency or increased IFN-γ. Example 41 of the '272 patent teaches the role of zalpha11 Ligand, particularly in combination with IL-15, in NK cells, a cell type with unclear significance in MS. Example 42 of the '272 patent simply explores the effect of zalpha11 on T cell proliferation. In fact, nowhere

does the '272 patent associate IL-21 with the modulation of IL-10 or IFN-γ, let alone teach the use of an IL-21/IL-21R agonist to suppress, reduce, delay, or ameliorate a symptom(s) of MS or any other IL-10-associated disorder(s). Moreover, the only place in which the '272 patent even mentions IL-10 or IFN-γ is in the "Background of the Invention" as examples of cytokines.

Finally, the Examiner has not satisfied the required burden of providing the evidence tending to show that the method described in the present claims is inherently present in the '272 patent. "'An invitation to investigate is not an inherent disclosure' where a prior art reference 'discloses no more than a broad genus of potential applications of its discoveries.'" M.P.E.P. § 2112(IV) at 2100-47 (quoting *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354,1367 (Fed. Cir. 2004). The '272 patent discloses a myriad of suggested possibilities for the use of zalpha11 Ligand. As previously discussed, the '272 patent does not specify whether an agonist or an antagonist of zalpha11 Ligand should be used for specific disorders. Therefore, the use of an agonist of IL-21 for the suppression, reduction, delay, or amelioration of a symptom(s) of MS or any other IL-10-associated disorder(s) would simply be a possibility, and not an inherent disclosure, in the '272 patent.

For at least these reasons, Applicants respectfully submit that the '272 patent does not, either expressly or inherently, anticipate the instant claims. Thus Applicants respectfully request reconsideration and withdrawal of the anticipation-based rejection.

VI. Rejection Under 35 U.S.C. § 103

A. The '272 Patent in View of the '549 Application and Kawai

The Examiner maintains the rejection of claims 1, 3-15, 17-19, and 29-34 under 35 U.S.C. 103(a) as allegedly being unpatentable over the '272 patent in view of U.S. Application Publication No. 2003/0108549, in the name of Carter et al. ("the '549 application"),

and Kawai et al., *Cell Immunol.* 171:262-68 (1996) ("Kawai"). Office Action, pp. 11-13. Applicants respectfully traverse this rejection.

The Examiner asserts that the '272 patent teaches the limitations of claims 1, 3, 4, 9-12, 14, and 29-34. *Id.* at p. 12. The Examiner also asserts that, although the '272 patent does not teach agonistic anti-IL-21R antibodies, the '549 application teaches an agonistic anti-IL-21R antibody in instant claims 1, 5, and 6 and a use of a combination of anti-inflammatory agents and anti-IL-21/IL-21R agonists to treat T cell-mediated disease such as tumor, as it relates to claims 7 and 8. *Id.* at pp. 12-13. The Examiner further asserts that the '549 application teaches the enhancement of T cell proliferation and cytokine regulation by IL-21/IL-21R agonists, which relates to ameliorating a symptom of MS associated with cytokines. *Id.* at p. 13. Finally, the Examiner asserts that, although the '272 patent and the '549 application do not teach injection of IL-21 agonists into the CNS, Kawai teaches intracerebroventricular and intrathecal administration routes. *Id.* Applicants respectfully disagree.

As Applicants explained in Section V above, the '272 patent does not teach the limitations of claims 1, 3, 4, 9-12, 14, and 29-34 because the '272 patent does not associate IL-21 with the modulation of IL-10 or IFN-γ and does not teach or suggest that an IL-21/IL-21R agonist would be useful to treat or ameliorate MS, a symptom of MS, or any other IL-10-associated disorder. Moreover, the '272 patent teaches that diseases such as MS "are the result of a complex network of immune dysfunction" while suggesting a myriad of possibilities for using IL-21. The '272 patent, col. 42, ll. 9-31. The disclosure of the '549 application and Kawai do not provide the missing elements of the '272 patent to reach the claimed invention.

For at least these reasons, Applicants respectfully submit that independent claims 1, 29, and 34, from which the remaining claims depend, are not obvious under 35 U.S.C. §103(a)

over the '272 patent in view of the '549 application and Kawai. Therefore, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

B. The '272 Patent in View of the '549 Application and Kawai, Further in View of Beebe

The Examiner maintains the rejection of claims 1, 3-15, 17-19, 29-36, and 38-40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '272 patent, the '549 application, and Kawai, and further in view of Beebe et al., *Cytokine and Growth Factor Rev.* 13:403-12 (2002) ("Beebe"). *Office Action*, pp. 13-14. Applicants respectfully traverse this rejection.

The Examiner asserts that the '272 patent teaches the limitations of claims 1, 3-15, 17-19, and 29-34. *Id.* at 14. The Examiner also asserts that Beebe provides a motivation and expectation of success in evaluating the level of IL-10 in MS patients before and after treatment because Beebe teaches that the level of IL-10 is low in MS. *Id.* Therefore, the Examiner concludes that it would have been obvious to a skilled artisan to ameliorate a symptom of MS regulated by inappropriate production of IL-10 and IFN-γ by incorporating the teachings of Beebe to measure/monitor the levels of IL-10 in MS patients while practicing the claimed method of the '272 patent, the '549 application, and Kawai. *Id.* Applicants respectfully disagree.

As discussed above, the '272 patent does not teach the limitations of claims 1, 3-15, 17-19, and 29-34, nor does the combination of the '272 patent, the '549 application, and Kawai. Beebe also does not cure the deficiencies of these references. Beebe only teaches that the level of IL-10 in MS patients is low.

For at least these reasons, Applicants respectfully submit that the instant claims are not obvious over the combination of the '272 patent, the '549 application, and Kawai, further

in view of Beebe and respectfully request reconsideration and withdrawal of the obviousness-based rejections of the claims.

## CONCLUSION

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns and rejections have been answered and overcome. Accordingly, reconsideration and allowance of all claims are earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

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